Complete Summary

GUIDELINE TITLE

(1) Chronic hepatitis B. (2) Corrections to AASLD guidelines on chronic hepatitis B.

BIBLIOGRAPHIC SOURCE(S)

Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007 Feb;45(2):507-39. [275 references] PubMed

Lok AS, McMahon BJ. Corrections to AASLD guidelines on chronic hepatitis B. Hepatology 2007 Jun;45(6):1347. [1 reference] PubMed

GUIDELINE STATUS

This is the current release of this guideline.

This guideline updates a previous version: Lok AS, McMahon BJ. Chronic hepatitis B. Alexandria (VA): American Association for the Study of Liver Diseases; 2004. 25 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references drugs for which important revised regulatory information has been released:

- August 16, 2007, Baraclude (Entecavir): Revisions to the prescribing information for Baraclude to indicate that the drug is not recommended for HIV/hepatitis B virus (HBV) co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) due to the potential for the development of HIV resistance.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic hepatitis B

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Prevention
Screening
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assist physicians and other health care providers in the recognition, diagnosis, and management of patients chronically infected with the hepatitis B virus (HBV)

TARGET POPULATION

- Individuals at risk for hepatitis B virus (HBV) infection
- Individuals with chronic HBV infection

Note: Management of hepatitis B in patients waiting for liver transplantation and prevention of recurrent hepatitis B post-liver transplant have been covered in a recent review article and will not be discussed in these guidelines.

INTERVENTIONS AND PRACTICES CONSIDERED

Screening, Counseling, Prevention

1. Screening for hepatitis B virus (HBV) in high-risk groups and vaccination, if negative
2. Counseling of carriers of HBV regarding prevention of transmission
3. Testing of sexual and household contacts of carriers for HBV and vaccination, if negative
4. Treatment of newborns of HBV-infected mothers with hepatitis B immune globulin (HBIG) and hepatitis B vaccine at delivery
5. Periodic testing of persons at risk for HBV infection for response to vaccination
6. Abstinence or limited use of alcohol in HBV carriers
7. Hepatitis B vaccination for persons who are positive only for hepatitis B core antibody (anti-HBc) and who are from a low endemic areas with no risk factors for HBV
8. Antiviral prophylaxis of hepatitis B carriers who receive immunosuppressive or cytotoxic therapy

Evaluation/Management

1. History and physical examination and family history of HBV infection and liver cancer
2. Laboratory tests including assessment of liver disease; tests for HBV replication; tests to rule out coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV), and human immunodeficiency virus (HIV) in those at risk; tests to screen for hepatocellular carcinoma (HCC) (alpha-fetoprotein [AFP] at baseline and, in high risk patients, ultrasound)
3. Vaccination for hepatitis A
4. HBV DNA assay
5. Liver biopsy
6. Evaluation for treatment of patients who have chronic HBV infection
7. Follow-up of patients not considered for treatment, including monitoring of alanine aminotransferase (ALT) and HBV DNA levels and screening tests for hepatocellular carcinoma in patients at high risk

Treatment

1. Treatment of chronic HBV
    - Pegylated (peg) interferon (IFN)-alpha
    - IFN-alpha
    - Lamivudine
    - Adefovir
    - Entecavir
    - Telbivudine
2. Treatment of drug-resistant HBV
3. Treatment of patients with HBV/HIV

4. Prophylactic antiviral therapy for HBV carriers at the onset of chemotherapy or immunosuppressive therapy
5. Treatment of symptomatic acute HBV
6. Treatment monitoring and discontinuation or adjustment of treatment as indicated

MAJOR OUTCOMES CONSIDERED

- Sensitivity, specificity, and diagnostic accuracy of screening tests
- Efficacy of treatment
- Adverse events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A formal review and analysis of published literature on hepatitis B (Medline search up to February 2006 and meeting abstracts in 2003–2005) was performed. In addition, the proceedings of the 2000 and 2006 National Institutes of Health conferences on the "Management of Hepatitis B", the European Association for the Study of the Liver (EASL) 2002 International Consensus Conference on Hepatitis B and the Asian-Pacific Consensus Statement on the Management of Chronic Hepatitis B: a 2005 Update, were considered in the development of these guidelines.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Grade I: Randomized controlled trials

Grade II-1: Controlled trials without randomization

Grade II-2: Cohort or case-control analytic studies

Grade II-3: Multiple time series, dramatic uncontrolled experiments

Grade III: Opinions of respected authorities, descriptive epidemiology

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. This committee provided extensive peer review of the manuscript. The guideline was approved by the American Association for the Study of Liver Diseases.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the American Association for the Study of Liver Diseases (AASLD): This guideline was originally published in 2001 and was updated most recently in February of 2007. Subsequently, a correction to the update was published in June 2007. The following recommendations reflect the complete updated guidelines.

Recommendations are followed by quality of evidence ratings (Grades I, II-1, II-2, II-3, III), which are defined at the end of the "Major Recommendations" field.

Screening High Risk Populations to Identify Hepatitis B Virus (HBV) Infected Persons

Recommendations for Persons Who Should Be Tested for HBV Infection

1. The following groups should be tested for HBV infection: persons born in hyperendemic areas (see Table below), men who have sex with men, persons who have ever used injecting drugs, dialysis patients, human immunodeficiency virus (HIV)-infected individuals, pregnant women, and family members, household members, and sexual contacts of HBV-infected persons. Testing for hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (anti-HBs) should be performed, and seronegative persons should be vaccinated. **(Grade I)**

Table. Groups at High Risk for HBV Infection Who Should be Screened

Individuals born in areas of high[2] and intermediate prevalence rates[3] for HBV including immigrants and adopted children[1,4] • Asia; all countries (except Sri Lanka) • Africa; all countries • South Pacific Islands; all countries and territories (except nonindigenous populations of New Zealand and Australia) • Middle East: all countries (except Cyprus) • Western Europe: Greece, Italy, Malta, Portugal, and Spain • Eastern Europe: all countries (except Hungary) • The Arctic: indigenous populations • South America: Argentina, Bolivia, Brazil, Ecuador, Guyana, Suriname, Venezuela, and Amazon region of Colombia and Peru • Central America: Belize, Guatemala, Honduras, and Panama • Caribbean: Antigua and Barbuda, Dominica, Dominican Republic, Grenada, Haiti, Jamaica, Puerto Rico, St. Kitts and Nevis, St. Lucia, St. Vincent and Grenadines, Trinidad and Tobago, and Turks and Caico
Other high-risk groups recommended for screening • Household and sexual contacts of HBsAg-positive persons[4] • Persons who have ever injected drugs[4] • Persons with multiple sexual partners or history of sexually transmitted disease[4] • Men who have sex with men[4] • Inmates of correctional facilities[4] • Individuals with chronically elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)[4] • Individuals infected with hepatitis C virus (HCV) or HIV[4] • Patients undergoing renal dialysis[4] • All pregnant women

[1] If HBsAG-positive persons are found in the first generation, subsequent generations should be tested.
[2] HBsAg prevalence >8%
[3] HBsAg prevalence 2 to 7%
[4] Those who are seronegative should receive hepatitis B vaccine.

Counseling and Prevention of Hepatitis B

Recommendations for Counseling and Prevention of Transmission of Hepatitis B from Individuals with Chronic HBV Infection

2. Carriers should be counseled regarding prevention of transmission of HBV (see the Table below). **(Grade III)**

Table. Recommendations for Infected Persons Regarding Prevention of Transmission of HBV to Others

Persons who are HBsAg-positive should

- Have sexual contacts vaccinated
- Use barrier protection during sexual intercourse if partner not vaccinated or naturally immune
- Not share toothbrushes or razors
- Cover open cuts and scratches
- Clean blood spills with detergent or bleach
- Not donate blood, organs, or sperms

Children and adults who are HBsAg-positive:

- Can participate in all activities including contact sports
- Should not be excluded from daycare or school participation and should not be isolated from other children
- Can share food, utensils, or kiss others

3. Sexual and household contacts of carriers who are negative for HBV seromarkers should receive hepatitis B vaccination. **(Grade III)**
4. Newborns of HBV-infected mothers should receive hepatitis B immune globulin (HBIG) and hepatitis B vaccine at delivery and complete the recommended vaccination series. **(Grade I)**
5. Persons who remain at risk for HBV infection such as infants of HBsAg-positive mothers, health care workers, dialysis patients, and sexual partners of carriers should be tested for response to vaccination. **(Grade III)**
    - Postvaccination testing should be performed at 9 to 15 months of age in infants of carrier mothers and 1 to 2 months after the last dose in other persons. **(Grade III)**
    - Follow-up testing of vaccine responders is recommended annually for chronic hemodialysis patients. **(Grade III)**
6. Abstinence or only limited use of alcohol is recommended in hepatitis B carriers. **(Grade III)**
7. Persons who are positive only for hepatitis B core antibody (anti-HBc) and who are from a low endemic area with no risk factors for HBV should be given the full series of hepatitis B vaccine. **(Grade II-2)**

Evaluation and Management of Patients with Chronic HBV Infection

Recommendations for Initial Evaluation of Persons with Chronic HBV Infection

8. Initial evaluation of persons newly diagnosed with chronic HBV infection should include history, physical examination, and laboratory testing as outlined in the Table below. **(Grade III)**

Table. Evaluation of Patients with Chronic HBV Infection

Initial Evaluation

1. History and physical examination
2. Family history of liver disease, hepatocellular carcinoma (HCC)
3. Laboratory tests to assess liver disease—complete blood counts with platelets, hepatic panel and prothrombin time
4. Tests for HBV replication—hepatitis B e antigen (HBeAg)/antibody to hepatitis B e antigen (anti-HBe), HBV DNA
5. Tests to rule out viral coinfections—antibody to hepatitis C virus (anti-HCV), antibody to hepatitis D virus (anti-HDV) (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV in those at risk
6. Tests to screen for HCC-alpha fetoprotein (AFP) at baseline and, in high risk patients, ultrasound
7. Consider liver biopsy to grade and stage liver disease—for patients who meet criteria for chronic hepatitis

9. All persons with chronic hepatitis B not immune to hepatitis A should receive 2 doses of hepatitis A vaccine 6 to 18 months apart. **(Grade II-3)**

Recommendations for Monitoring Patients with Chronic HBV Infection (See Figure 1 in the original guideline document.)

10. HBeAg-positive and HBeAg-negative patients who meet criteria for chronic hepatitis B (see Table below) should be evaluated for treatment. **(Grade I)**

Table. Diagnostic Criteria of HBV Infection

Chronic Hepatitis B

1. HBsAg+ >6 months
2. Serum HBV DNA >20,000 IU/mL (10^5 copies/mL), lower values 2,000 to 20,000 IU/mL (10^4 to 10^5 copies/mL) are often seen in HBeAg-negative chronic hepatitis B
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

Inactive HBsAg Carrier State

1. HBsAg+ >6 months
2. HBeAg-, anti-HBe+
3. Serum HBV DNA <2,000 IU/mL

4. Persistently normal ALT/AST levels
5. Liver biopsy confirms absence of significant hepatitis

Resolved Hepatitis B

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs
2. HBsAg-
3. Undetectable serum HBV DNA*
4. Normal ALT levels

*Very low levels may be detectable using sensitive polymerase chain reaction (PCR) assays

11. HBeAg-positive patients:
    - HBeAg-positive patients with persistently normal ALT should be tested for ALT at 3- to 6-month intervals. ALT along with HBV DNA should be tested more often when ALT levels become elevated. HBeAg status should be checked every 6 to 12 months. **(Grade III)**
    - Patients who remain HBeAg positive with HBV DNA levels >20,000 IU/mL after a 3- to 6-month period of elevated ALT levels between 1 to 2 times the upper limit of normal (ULN), or who remain HBeAg positive with HBV DNA levels >20,000 IU/mL and are >40 years old, should be considered for liver biopsy, and treatment should be considered if biopsy shows moderate/severe inflammation or significant fibrosis. **(Grade III)** Patients who remain HBeAg positive with HBV DNA levels >20,000 IU/mL after a 3- to 6-month period of elevated ALT levels >2 x ULN should be considered for treatment. **(Grade III)**.

12. HBeAg-negative patients:
    - HBeAg-negative patients with normal ALT and HBV DNA <2,000 IU/mL should be tested for ALT every 3 months during the first year to verify that they are truly in the "inactive carrier state" and then every 6 to 12 months. **(Grade III)**
    - Tests for HBV DNA and more frequent monitoring should be performed if ALT or AST increases above the normal limit. **(Grade III)**

Recommendations for HCC Screening

13. HBV carriers at high risk for HCC such as Asian men over 40 years and Asian women over 50 years of age, persons with cirrhosis, persons with a family history of HCC, Africans over 20 years of age, and any carrier over 40 years with persistent or intermittent ALT elevation and/or high HBV DNA level >2,000 IU/mL should be screened with ultrasound (US) examination every 6-12 months. **(Grade II-2)**
14. For HBV carriers at high risk for HCC who are living in areas where US is not readily available, periodic screening with AFP should be considered. (**Grade II-2)**

Treatment of Chronic Hepatitis B

Recommendations on Whom to Treat and with What Antiviral Agent (see Table 12 in the original guideline document.)

15. Patients with HBeAg-positive chronic hepatitis B
    a. *ALT greater than 2 times normal or moderate/severe hepatitis on biopsy, and HBV DNA >20,000 IU/mL.* These patients should be considered for treatment. **(Grade I)**
        - Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs. **(Grade II-2)**
        - Patients with icteric ALT flares should be promptly treated. **(Grade III)**
        - Treatment may be initiated with any of the 6 approved antiviral medications, but pegylated (peg) interferon (IFN)-alpha, adefovir, or entecavir are preferred. **(Grade I)**

    b. *ALT persistently normal or minimally elevated (<2 times normal).* These patients generally should not be initiated on treatment. **(Grade I)**
        - Liver biopsy may be considered in patients with fluctuating or minimally elevated ALT levels especially in those above 40 years of age. **(Grade II-3)**
        - Treatment may be initiated if there is moderate or severe necroinflammation or significant fibrosis on liver biopsy. **(Grade I)**

    c. *Children with elevated ALT greater than 2 times normal.* These patients should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months. **(Grade I)**
        - Treatment may be initiated with IFN-alpha or lamivudine. **(Grade I)**

16. Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA >20,000 IU/mL and elevated ALT >2 times normal) should be considered for treatment. **(Grade I)**
    - Liver biopsy may be considered for HBeAg-negative patients with lower HBV DNA levels (2,000 to 20,000 IU/mL) and borderline normal or minimally elevated ALT levels. **(Grade II-2)**
    - Treatment may be initiated if there is moderate/severe inflammation or significant fibrosis on biopsy. **(Grade I)**
    - Treatment may be initiated with any of the 6 approved antiviral medications but pegIFN-alpha, adefovir, or entecavir are preferred in view of the need for long-term treatment. (**Grade I for pegIFN-alpha, adefovir, entecavir, and telbivudine and Grade II-1 for IFN-alpha and lamivudine)**

17. Patients who failed to respond to prior IFN-alpha (standard or pegylated) therapy may be retreated with nucleoside analogues (NA) if they fulfill the criteria listed above. **(Grade I)**
18. Patients who failed to achieve primary response as evidenced by <2 log decrease in serum HBV DNA level after at least 6 months of NA therapy should be switched to an alternative treatment. **(Grade III)**

19. Patients who develop breakthrough infection while receiving NA therapy (see Table below)
    - Compliance should be ascertained, and treatment resumed in patients who have had long lapses in medications. **(Grade III)**
    - A confirmatory test for antiviral-resistant mutation should be performed if possible to differentiate primary non-response from breakthrough infection and to determine if there is evidence of multi-drug resistance (in patients who have been exposed to more than one NA treatment). **(Grade III)**
    - All patients with virologic breakthrough should be considered for rescue therapy. **(Grade II-2)**
    - For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares. **(Grade III)**

Table. Management of Anti-Viral Resistant HBV

Prevention • Avoid unnecessary treatment • Initiate treatment with potent antiviral that has low rate of drug resistance or with combination therapy • Switch to alternative therapy in patients with primary non-response *Monitoring* • Test for serum HBV DNA (PCR assay) every 3 to 6 months during treatment • Check for medication compliance in patients with virologic breakthrough • Confirm antiviral resistance with genotypic testing	
Treatment	
Lamivudine-resistance	Add adefovir or tenofovir Stop lamivudine, switch to Truvada[1,3] Stop lamivudine, switch to entecavir (preexisting lamivudine-resistant mutation predisposes to entecavir resistance)[2]
Adefovir-resistance	Add lamivudine[2] Stop adefovir, switch to Truvada[1,3] Switch to or add entecavir[2,3]
Entecavir-resistance	Switch to or add adefovir or tenofovir[3]

Telbivudine-resistance[4]	Add adefovir or tenofovir Stop telbivudine, switch to Truvada Stop telbivudine, switch to entecavir (preexisting telbivudine-resistant mutation predisposes to entecavir resistance)

[1] Truvada = combination pill with emtricitabine 200 mg and tenofovir 300 mg
[2] Durability of viral suppression unknown, especially in patient with prior lamivudine resistance
[3] In HIV coinfected persons; scanty in vivo data in non-HIV infected persons
[4] Clinical data not available

20. Treatment of patients with lamivudine (or telbivudine)-resistant HBV
    a. If adefovir is used, lamivudine (or telbivudine) should be continued indefinitely to decrease the risk of hepatitis flares during the transition period and to reduce the risk of subsequent adefovir resistance. **(Grade II-3 for lamivudine-resistant HBV and Grade III for telbivudine-resistant HBV)**
    b. If entecavir is used, lamivudine or telbivudine should be stopped as continued presence of lamivudine (or telbivudine)-resistant mutations will increase the risk of entecavir resistance. **(Grade II-3 for lamivudine-resistant HBV and Grade III for telbivudine-resistant HBV)**

21. Treatment of patients with adefovir-resistant HBV
    a. In patients with no prior exposure to other NA, lamivudine or entacavir may be added. **(Grade III)**
    b. In patients with prior lamivudine resistance in whom lamivudine had been stopped when treatment was switched to adefovir, lamivudine may be added but the durability of response is unknown and reemergence of lamivudine-resistant mutations has been reported. **(Grade II-2)**

22. Treatment of patients with entecavir-resistant HBV
    a. Adefovir can be used as it has been shown to have activity against entecavir-resistant HBV in in vitro studies, but clinical data are lacking. **(Grade II-3)**

23. Patients with compensated cirrhosis—Treatment should be considered for patients with ALT >2 times normal, and for patients with normal or minimally elevated ALT if serum HBV DNA levels are high (>2,000 IU/mL). **(Grade II-2)**
    a. Patients with compensated cirrhosis are best treated with NAs because of the risk of hepatic decompensation associated with IFN-alpha-related flares of hepatitis. In view of the need for long-term therapy, adefovir or entecavir is preferred. **(Grade II-3)**

24. Patients with decompensated cirrhosis—Treatment should be promptly initiated with a NA that can produce rapid viral suppression with low risk of drug resistance. **(Grade II-1)**

a. Lamivudine or adefovir may be used as initial treatment preferably in combination to reduce the risk of drug resistance and to achieve rapid virus suppression. **(Grade II-2)** Telbivudine may be substituted for lamivudine but clinical data documenting its safety and efficacy in patients with decompensated cirrhosis are lacking.
b. Entecavir would be an appropriate treatment in this setting but clinical data documenting its safety and efficacy in patients with decompensated cirrhosis are lacking. **(Grade III)**
c. Treatment should be coordinated with a transplant center. **(Grade III)**
d. IFN-alpha/pegIFN-alpha should not be used in patients with decompensated cirrhosis. **(II-3)**

25. In patients with inactive HBsAg carrier state antiviral treatment is not indicated, but these patients should be monitored (see Recommendation 12). **(Grade II-2)**

Dose Regimens

26. IFN-alpha and pegIFN-alpha are administered as subcutaneous injections.
    a. The recommended dose of standard IFN-alpha for adults is 5 MU daily or 10 MU thrice weekly. The recommended dose of pegIFN-alpha2a is 180 mcg weekly. **(Grade I)**
    b. The recommended IFN-alpha dose for children is 6 MU/m^2 thrice weekly with a maximum of 10 MU. **(Grade I)** PegIFN-alpha has not been approved for treatment of chronic hepatitis B in children.
    c. The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks for standard IFN-alpha and 48 weeks for pegIFN-alpha. **(Grade I)**
    d. The recommended treatment duration for HBeAg-negative chronic hepatitis B is 48 weeks for both standard and peg-IFN-alpha **(Grade II-3)**

27. Lamivudine is administered orally.
    a. The recommended lamivudine dose for adults with normal renal function and no HIV coinfection is 100 mg daily **(Grade I)**. Dose adjustment is needed for patients with estimated glomerular filtration rate <50 mL/min (see Table 10a in the original guideline document). **(Grade I)**
    b. The recommended lamivudine dose for children is 3 mg/kg/day with a maximum of 100 mg/day. **(Grade I)**
    c. The recommended dose of lamivudine for persons co-infected with HIV is 150 mg twice daily. Lamivudine should only be used in combination with other antiretroviral medications. **(Grade I)**

28. Adefovir is administered orally.
    a. The recommended adefovir dose for adults with normal renal function is 10 mg daily. **(Grade I)** Dose adjustment is needed for patients with estimated glomerular filtration rate <50 mL/min (see Table 10b in the original guideline document).

29. Entecavir is administered orally.

a. The recommended entecavir dose for adults with normal renal function is 0.5 mg daily for patients with no prior lamivudine treatment, and 1.0 mg daily for patients who are refractory/resistant to lamivudine. **(Grade I)**
b. Dose adjustment is needed for patients with estimated glomerular filtration rate <50 mL/min (see Table 10c in the original guideline document).

30. Telbivudine is administered orally.
    a. The recommended dose for adults with normal renal function is 600 mg daily. **(Grade I)** Dose adjustment is needed for patients with estimated glomerular filtration rate <50 mL/min (see Table 10d in the addendum to the original guideline document).

31. Duration of nucleoside analogue treatment
    a. HBeAg-positive chronic hepatitis B—Treatment should be continued until the patient has achieved HBeAg seroconversion and completed at least 6 months of additional treatment after appearance of anti-HBe. **(Grade I)**
        - Close monitoring for relapse is needed after withdrawal of treatment. **(Grade I)**

    b. HBeAg-negative chronic hepatitis B—Treatment should be continued until the patient has achieved HBsAg clearance. **(Grade I)**
    c. Compensated cirrhosis—These patients should receive long-term treatment. However, treatment may be stopped in HBeAg-positive patients if they have confirmed HBeAg seroconversion and have completed at least 6 months of consolidation therapy and in HBeAg-negative patients if they have confirmed HBsAg clearance. **(Grade II-3)**
        - Close monitoring for viral relapse and hepatitis flare is mandatory if treatment is stopped. **(Grade II-3)**

    d. Decompensated cirrhosis and recurrent hepatitis B post-liver transplantation - Life-long treatment is recommended. **(Grade II-3)**

Special Populations

Recommendations for Treatment of Patients with HBV/HIV Coinfection

32. Patients who meet criteria for chronic hepatitis B should be treated. **(Grade III)**
    - Liver biopsy should be considered in patients with fluctuating or mildly elevated ALT (1 to 2 x normal). **(Grade II-3)**

33. Patients who are not on highly active anti-retroviral therapy (HAART) and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as pegIFN-alpha, adefovir, or entecavir. Caution should be exercised if entecavir is used in this setting. Although telbivudine does not target HIV, it should not be used in this circumstance. **(Grade II-3)**

34. Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred. **(Grade II-3)**
35. Patients who are already on effective HAART that does not include a drug active against HBV may be treated with pegIFN alpha, adefovir, or entecavir. **(Grade II-3)**
36. In patients with lamivudine resistance, tenofovir or adefovir should be added. **(Grade III)**
37. When HAART regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV, unless the patient has achieved HBeAg seroconversion and has completed an adequate course of consolidation treatment. **(Grade II-3)**

Antiviral Prophylaxis of Hepatitis B Carriers Who Receive Immunosuppressive or Cytotoxic Chemotherapy

Recommendations for Treatment of Hepatitis B carriers Who Require Immunosuppressive or Cytotoxic Therapy

38. HBsAg testing should be performed in patients who are at high risk of HBV infection (see recommendation number 1), prior to initiation of chemotherapy or immunosuppressive therapy. **(Grade II-3)**
39. Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy.
    a. Patients with baseline HBV DNA <2,000 IU/mL level should continue treatment for 6 months after completion of chemotherapy or immunosuppressive therapy. **(Grade III)**
    b. Patients with high baseline HBV DNA (>2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients. **(Grade III)**
    c. Lamivudine or telbivudine can be used if the anticipated duration of treatment is short ($\leq$12 months). **(Grade I for lamivudine and Grade III for telbivudine)**
    d. Adefovir or entecavir is preferred if longer duration of treatment is anticipated. Entecavir has more rapid onset of action than adefovir and may be more appropriate in this setting. **(Grade III)**
    e. IFN-alpha should be avoided in view of the bone marrow suppressive effect. **(Grade II-3)**

Recommendations for Treatment of Patients with Acute Symptomatic Hepatitis B

40. Treatment is only indicated for patients with fulminant hepatitis B and those with protracted, severe acute hepatitis B. **(Grade III)**
41. Lamivudine, telbivudine, or entecavir is preferred. **(Grade II-3)**
    a. Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. **(Grade II-1)**
    b. IFN-alpha is contraindicated. **(Grade III)**

Definitions:

Quality of Evidence

Grade I: Randomized controlled trials

Grade II-1: Controlled trials without randomization

Grade II-2: Cohort or case-control analytic studies

Grade II-3: Multiple time series, dramatic uncontrolled experiments

Grade III: Opinions of respected authorities, descriptive epidemiology

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for follow-up of hepatitis B virus (HBV) carriers who are hepatitis B e antigen (HBeAg)-positive and HBeAg-negative.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is specifically stated for selected recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Effective screening for hepatitis B virus (HBV)
- Prevention of transmission of HBV
- Effective treatment of HBV, including suppression of HBV replication, increased hepatitis B e antigen (HBeAg) seroconversion, decreased HBeAg reversion, and decreased HBV relapse
- Effective treatment of relapsed HBV
- Decreased development and progression of HBV-related liver disease
- Improved overall survival and survival free of hepatic decompensation

POTENTIAL HARMS

Standard or Pegylated (peg) Interferon-alpha (IFN)

- The most common side effect is an initial influenza-like illness: fever, chills, headache, malaise and myalgia. Other common side effects include fatigue, anorexia, weight loss, and mild increase in hair loss.
- IFN-alpha has myelosuppressive effects but significant neutropenia ($<1000/mm^3$) or thrombocytopenia ($<50,000/mm^3$) are uncommon except in patients who have decreased cell counts prior to treatment.
- IFN-alpha treatment is accompanied by flare in alanine aminotransferase (ALT) in 30 to 40% of patients. Hepatitis flares are considered to be an indicator of a favorable response but they can lead to hepatic decompensation, especially in patients with underlying cirrhosis.

- The most troublesome side effect of IFN-alpha is emotional lability: anxiety, irritability, depression, and suicidal tendency.
- IFN-alpha has been reported to induce the development of a variety of autoantibodies. In most instances, this is not accompanied by clinical illness. However, both hyper- and hypothyroidism that require treatment have been reported.
- Rarely, retinal changes and impaired vision have been reported.

Lamivudine

Various adverse events including a mild (2- to 3-fold) increase in ALT level have been reported in patients receiving lamivudine, but these events occurred in the same frequency among the controls.

Adefovir

Nephrotoxicity has been reported in 3% of patients with compensated liver disease after 4 to 5 years of continued adefovir therapy, and in 12% of transplant recipients and 28% of patients with decompensated cirrhosis during the first year of therapy.

Entecavir

Similar safety profile as lamivudine

Telbivudine

Safety profile comparable to lamivudine

CONTRAINDICATIONS

CONTRAINDICATIONS

- Interferon (IFN)-alpha is contraindicated in patients with symptomatic acute hepatitis B because of the risks of worsening hepatitis and the frequent side effects.
- IFN-alpha/pegylated (peg)IFN-alpha should not be used in patients with decompensated cirrhosis.
- Telbivudine should not be used in hepatitis B virus (HBV)/human immunodeficiency virus (HIV) coinfected patients.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These recommendations suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007 Feb;45(2):507-39. [275 references] PubMed

Lok AS, McMahon BJ. Corrections to AASLD guidelines on chronic hepatitis B. Hepatology 2007 Jun;45(6):1347. [1 reference] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Dec (revised 2007 Feb; addendum released 2007 Jun)

GUIDELINE DEVELOPER(S)

American Association for the Study of Liver Diseases - Private Nonprofit Research Organization

SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

GUIDELINE COMMITTEE

Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Anna S. F. Lok, Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, MI; Brian J. McMahon, Liver Disease and Hepatitis Program, Alaska Native Medical Center and Arctic Investigations Program, Centers for Disease Control, Anchorage, AK

Committee Members: Margaret C. Shuhart, MD, MS (*Chair*); Andres Cardenas, MD, MMSc; Stanley M. Cohen, MD; Timothy J. Davern, MD; Steven L. Flamm, MD; Steven-Huy B. Han, MD; Charles D. Howell, MD; David R. Nelson, MD; K. Rajender Reddy, MD; Bruce A. Runyon, MD; John B. Wong, MD; Nizar N. Zein, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. McMahon's spouse owns stock in GlaxoSmith-Kline. Dr. Lok is a consultant for, received grants, and is on the Scientific Advisory Board of, Bristol-Myers Squibb, GlaxoSmithKline, Idenix, Roche, Gilead, and Innogenetics. She is also on the Scientific Advisory Board of Pharmasset. Dr. Lok received grants from Schering-Plough. Please refer to www.aasld.org for disclosures by Practice Guidelines Committee members.

ENDORSER(S)

Infectious Diseases Society of America - Medical Specialty Society

GUIDELINE STATUS

This is the current release of this guideline.

This guideline updates a previous version: Lok AS, McMahon BJ. Chronic hepatitis B. Alexandria (VA): American Association for the Study of Liver Diseases; 2004. 25 p.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site.

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org; e-mail: aasld@aasld.org.

AVAILABILITY OF COMPANION DOCUMENTS

This guideline is available as a Personal Digital Assistant (PDA) download via the APPRISOR™ Document Viewer from www.apprisor.com.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 9, 2003. The information was verified by the guideline developer as of June 12, 2003. The summary was updated by ECRI on July 27, 2004. The updated information was verified by the guideline developer as of August 25, 2004. This NGC summary was updated by ECRI Institute on June 12, 2007. The updated information was verified by the guideline developer on August 22, 2007.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 9/15/2008